

RESTRICTION REQUIREMENT

The Examiner has stated that the process of the present invention can be used to form a materially different product such as a hydroxyethylated polysaccharide e. g. cellulose. While this assertion has some truth, its practical application is unclear at this point to Applicants. In principle, every polymer carrying a hydroxy group and every substance with the appropriate functional group can be hydroxyethylated with ethylene oxide. This is not the problem of the present invention. The subject matter of this invention is not simply reaction of ethylene oxide with starch, but rather the essential issue of forming a particular distribution of substituents i.e. the particular attainment of the designated HES product with the recited molecular weight, MS, DS and the particular relationship of C2 to C6. It is therefore submitted the Examiner's reasoning does not support the restriction requirement.

SECTION 103 REJECTION

Applicants acknowledge that the rejection of Claims 1-3 as obvious over U. S. patent 4,629,698 is expressly withdrawn by the Examiner. Claim 1-3 and 8-11 are however, now rejected as obvious over reference A, U. S. patent 4,629,698 (Nitsch, et al.) taken with reference L, British patent 935,339 (Staley) and British patent 1 395 777 (Morishita).

The Examiner characterizes the references as follows. Nitsch et al. teaches certain HES, but not the C2:C6 ratio or the DS value of the claimed invention. Staley is said to concern production of HES and to teach it is known how to manipulate substitution of HES. Morishita is also said to concern production of HES and to teach how to manipulate the C2:C6 substitution ratio.

Applicants submit Nitsch, et al. not only has the deficiencies conceded by the Examiner (being silent as to DS value and C2/C6 ratio) but that it uses a process having two major differences from that which Applicants claim. The first difference is that

hydrolysis takes place at least in part enzymatically. In the instant invention, acid hydrolysis is used. Acid hydrolysis is a process which runs statistically, while enzymatic hydrolysis as carried out in Nitsch et al. cleaves only the alpha-1,4 bonds. Enzymatic hydrolysis thus gives a totally different branching pattern and results in an HES having different properties from that produced by acid hydrolysis.

The second process difference is the pH of hydroxyethylation. From the parameters of Nitsch et al. Examples 1 and 3, one may calculate that hydroxyethylation is carried out at a pH clearly above 13. In contrast, the pH during hydroxyethylation in the claimed invention is held substantially at 12. This means the HES product from the present invention contains a high relationship of C2/C6. This cannot be obtained by the process of Nitsch et al. It is clear that unless Nitsch et al. and the secondary references can be shown to overcome these discrepancies, as well as the silence on C2:C6 and DS value, the rejection of the claimed invention cannot stand.

Turning to the secondary references, Applicants traverse the Examiner's assertion that Staley concerns HES and the Examiner's opinion that Staley discloses, at page 1, lines 52-60, the preparation of a hydroxyethyl starch derivative. Actually, Staley is restricted solely to hydroxy alkyl amylose made from the amylose fraction of starch (see page 1, line 23 to 26). Staley is totally silent on use of branched starch fraction (amylopectin), which is the only starch fraction having medical use. Furthermore, the use of Staley's hydroxylalkyl amylose is not described as having medical uses.

In fact, the teachings in Staley would lead one to conclude that its amylose cannot be used as a plasma expander. Staley is concerned solely with those parameters which are relevant to the use of hydroxy amylose as a film binder, namely retrogradation, swellability, water solubility and film binding ability (see page 2, lines 23-29). The Staley amylose fraction is insoluble in water at a temperature under 100°C (page 2, lines 98-108). Clearly, such a composition would be unsuitable for use as a plasma expander, which will usually have a temperature in use of not much greater than 96.8°F.

Moreover, the process of Staley is quite different from that of Claims 8-11. The hydroxy alkylation is carried out on a suspended amylose wherein the integrity of the starch particles is maintained (see page 2, lines 83 to 87). For the formation of the hydroxy alkyl amyloses, it is clear that no pre-treated amyloses are utilized. This is in direct contrast to the medical requirements for as hydroxy ethyl starch-based plasma expander.

Given these differences, it is submitted no motivation exists to combine Staley with Nitsch et al.; and that, on the contrary, a person having skill in the art would avoid doing so. Even if one were to combine the references, Staley is silent regarding the C2/C6 substitution ratio or the molecular weight range of the claimed invention. Because Staley fails to provide crucial teachings, and is directed to amylose, it is clear that if the references were combined, they could not lead to the claimed invention.

Turning to Morishita, Applicants traverse the Examiner's assertion that the reference teaches how to control the C2:C6 ratio in HES. This is an overgeneralization. Actually, Morishita teaches a HES (and a process for making it) having a C2:C6 ratio of from 0.5 to 2.0 -- far less than the 8-20 ratio of Claim 1. By teaching how to make HES having this lower ratio, the reference does not teach how to produce a C2:C6 ratio of 8-20.

The Examiner attempts to overcome the absence of such a teaching by stating the 0.5-2.0 ratio is the same as 5-20. Applicants traverse the Examiner's assertion that the C2 to C6 molar relationship of 0.5 to 2.0 in Morishita is equivalent to 5 to 20. Actually, the teachings of Morishita reveal a strong preference for greater substitution at C6 than at C2 (page 1, lines 13-15; page 2, lines 1-7 and 17-20).

The Examiner's argument for his assertion is invalid. Under certain limited conditions, the range of 0.5 to 2.0 may be considered equivalent to 5 to 20. Here, however, Morishita quite clearly teaches that the relationship of the C2 substitution to the

C6 substitution should lie between 0.5 to 2.0 and also that carbon atom 6 should be more strongly substituted by hydroxyethyl residues than carbon atom 2. It is quite clear from Morishita that 0.5 to 2.0 means nothing other than 0.5/1 to 2/1; and 0.5/1 means carbon atom 2 carries one substituent and carbon atom 6 carries two substituents; and 2/1 means carbon atom 2 carries two substituents and carbon atom 6 carries only one substituent. By converting the range 0.5 to 2.0 to 5 to 20, the Examiner creates a totally different substitution pattern, namely one with far more substitution at carbon atom 2 than at carbon atom 6. This is distinctly disfavored in Morishita. As a result it is quite clear that the range recited in Morishita does not overlap the C2/C6 range of the claimed invention.

Not surprisingly, these different C2:C6 ratios affect the synthetic protocols of Morishita and the claimed invention. In Morishita, a molar ratio of alkali to starch of at least 2.0 is used to deliver the desired product. In contrast thereto, the process of the present invention uses a pH of about 12, which corresponds to a alkali: starch ratio of between 1:8 to 1:1.2. This is a clear difference between the two processes.

Further traversing the Examiner's assertion that Morishita teaches how to control the C2-C6 relationship, Applicants point out the following:

1. From Table 1 on page 4, the data show that there was clearly no success under the recited conditions to obtain a constant substitution level over the entire alkali starch range. Clearly, the desired substitution level is directly dependent upon the alkali starch relationship. Furthermore, Morishita teaches that the C2/C6 relationship depends very strongly upon the addition of organic bases (see page 5, line 17 through page 6, line 13 and upon inorganic salts see page 6, lines 14-16).

2. The reaction of starch with the hydroxy ethylating agent is carried out in Morishita at elevated temperatures and correspondingly short reaction times whereas in the process of the present invention, one works with temperatures of 20-25°C and longer reaction times which influences the reaction kinetic.

3. In Morishita which utilizes a low alkali starch relationship, a high C2/C6 ratio results (10, 8 and 9,8) (See Table 1 on page 4 of Morishita). This high ratio is a substitution level which is outside the claimed DS range of the HES product herein.

4. Experimental work carried out on the HES product of the present invention with respect to its suitability as a plasma expander leads to an opposite conclusion to that taught by Morishita; i.e., by providing a size substitution at C2 with respect to the substitution at C6, the kinetic is improved.

Morishita teaches that its HES with its 0.5 to 2.0 ratio of C2:C6 has certain advantages. There is no teaching that a ratio of 8 to 20 is desirable, much less how one would produce HES having such a different substitution pattern. Thus, it is clear that even if Nitsch et al., Staley and Morishita were combined, one would be led away from the claimed HES and the process for making it.

Applicants submit the Examiner's reading of the references appears to have been flawed by reliance on hindsight. Several elements of the claimed invention have been identified in the prior art. However, there is no motivation to combine the references as the Examiner proposes; and even if they were so combined, it appears the combination would lead neither to Applicants' claimed HES nor the claimed process.

APPLICANTS' DECEMBER 20, 1991 DECLARATION

The Examiner found Applicants' December 20, 1991 Declaration insufficient to overcome the rejection based on Nitsch et al. because the Declaration "is not germane to the rejection at issue" (Official Action, page 5, paragraph 2). Applicants traverse this statement as well as the treatment of their Declaration. First, Applicants submit the Declaration was highly germane to the obviousness rejection, as it demonstrated the surprising superiority (in rapid excretion time) over the seemingly similar HES of Nitsch et al. More importantly however, Applicants traverse the Examiner's treatment of the



Declaration as being tantamount to dismissal without giving the Declaration due consideration. Evidence of ~~dis~~ surprising quality constitutes part of the subject matter of the invention as a whole. Further, the improved excretion time of the claimed HES is a long sought improvement in plasma expanders. Thus, Applicants' Declaration set out a secondary indicator of non-obviousness as well as an aspect of the invention, neither of which may be overlooked in an obviousness analysis. Applicants request the Examiner therefore to give the Declaration the full consideration to which it is due.

For these reasons, reconsideration and withdrawal of the obviousness rejection are requested. As no further obstacle to allowance of the claims appears to exist, the Examiner is requested to pass the claims to issue.

Respectfully submitted,

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22nd June 1992
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